Notice of Allowability	Application No.	Applicant(s)	
	10/650,057	VON KNEBEL DOEBERITZ ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *26 June 2007*.

2. ☒ The allowed claim(s) is/are *1-6,20,21 and 23-28*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20070907* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

2. Authorization for this examiner's amendment was given in a telephone interview with Viola T. Kung, Ph.D., on September 7, 2007.

3. The application has been amended as follows:

In the claims:

The following set of claims has replaced the prior set of claims, which was submitted as part of the amendment filed June 26, 2007:

Claim 1. (Currently Amended) A method for detecting cervical carcinomas, cervical intraepithelial ~~neoplasias~~ neoplasms or cervical carcinomas in situ in a human subject, the method ~~comprises~~ comprising the steps of: (a) obtaining a cervical body sample from the human subject, (b) solubilizing the cervical body sample in an aqueous lysis buffer comprising 0.1-1% SDS, and (c) reacting the solubilized cervical sample in the aqueous lysis buffer comprising 0.1-1% SDS with an antibody against cyclin dependent kinase inhibitor p16, and (d) determining the overexpression of cyclin dependent kinase inhibitor p16 in the solubilized cervical sample by comparing the level of cyclin dependent kinase inhibitor p16 within said solubilized cervical sample with the level present in a solubilized healthy human cervical sample, wherein cervical intraepithelial neoplasms or cervical carcinomas in the human subject are detected if overexpression of cyclin dependent kinase inhibitor p16 in the solubilized cervical sample is determined.

Claim 2. (Original) The method according to Claim 1, wherein the level of cyclin dependent kinase inhibitor p16 in the healthy human cervical body sample is provided as a predetermined value to set up a threshold for the detection procedure.

Claim 3. (Original) The method according to Claim 1, wherein the level of cyclin dependent kinase inhibitor p16 in a healthy human cervical sample is determined from a standardized sample solution, or from a representative number of healthy human cervical samples.

Claim 4. (Currently Amended) The method according to Claim 3, ~~and~~ wherein the determination of the level of cyclin dependent kinase inhibitor p16 in a healthy human cervical sample is carried out: a. in the course of the detection procedure, b. upon calibration of the detection system, c. once for each lot of detection reagents, or d. as a standard value for the detection method.

Claim 5. (Original) The method according to Claim 1, wherein the cervical body sample is swab, smear, aspirate, biopsy, preserved cytological specimen, histological specimen, fixed cell preparation or fixed tissue preparation.

Claim 6. (Original) The method according to Claim 1, wherein the cervical sample is solubilized: a. immediately after obtaining the sample, b. after storage and/or transport in a storage buffer, or c. after transport in a transportation buffer.

Claims 7-19. (Cancelled)

Claim 20. (Currently Amended) The method according to Claim 1, wherein the lysis buffer further comprises one or more <u>additional non-ionic or anionic</u> detergents.

Claim 21. (Previously Presented) The method according to Claim 1, wherein the lysis buffer further comprises a proteinase inhibitor.

Claim 22. (Cancelled)

Claim 23. (Previously Presented) The method according to Claim 1, wherein the overexpression of cyclin dependent kinase inhibitor p16 in the solubilized cervical sample is determined by an ELISA.

Claim 24. (Previously Presented) The method according to Claim 1, wherein the overexpression of cyclin dependent kinase inhibitor p16 in the solubilized cervical sample is determined by a lateral flow assay.

Claim 25. (Currently Amended) The method according to Claim 1, wherein the overexpression of cyclin dependent kinase inhibitor p16 in the solubilized cervical sample is determined by an ~~immulogical~~ immunological ~~assays~~ assay selected from the group consisting of EIA, ELISA, RIA, FIA, and lateral flow assay.

Claim 26. (Previously Presented) The method according to Claim 20, wherein at least one of said non-ionic ~~detergent~~ detergents is t-octylphenoxypolyethoxyethanol.

Claim 27. (New) The method according to Claim 1, wherein said aqueous lysis buffer comprises 0.1% SDS.

Claim 28. (New) The method according to Claim 1, wherein said aqueous lysis buffer comprises 0.4 % SDS.

Examiner's Statement of Reasons for Allowance

4. The following is an examiner's statement of reasons for allowance:

Support for the amendment to claim 1 and the addition of claims 27 and 28 is found in the specification, as originally filed; see, e.g., page 15, Table 1, which lists buffers comprising such varying concentrations of SDS. The specification discloses that lysis buffers comprising

concentrations of SDS in the range of 0.1-1% (w/v) are suitable for use in the disclosed process of detecting intraepithelial neoplastic cells or cervical carcinoma cells in a sample acquired from a subject by directly contacting the cervical body sample in the lysis buffer comprising the indicated concentration of SDS with an antibody that binds p16, so as to determine if p16 is overexpressed in the cells of the sample, as compared to normal cervical cells, and thereby detect the presence of intraepithelial neoplastic cells or cervical carcinoma cells in the subject's cervical body sample since, as disclosed, such cells are characterized by their overexpression of p16, relative to their normal counterpart.

During negotiation, Applicant's representative explained to the Examiner that the term "in situ" was inadvertently and unintentionally struck from claim 1 by the amendment filed February 15, 2007; the term finds support in the original claim 1.

The claims are directed to a process comprising contacting a sample of lysed cells containing solublized protein in an aqueous buffer comprising SDS with an antibody that binds p16; thus, the antibody-antigen binding assay is performed in the very lysis buffer used to lyse the cells of which the sample is comprised and solubilize the protein. As Applicant has remarked at page 9 of the amendment filed June 26, 2007, although one of the references cited as prior art discloses lysing cells with a lysis buffer containing SDS, none of the cited references teaches or suggests carrying out such an antibody-antigen binding assay in the presence of SDS. Applicant has further noted that, because SDS is a harsh detergent that causes proteins to denature, it would be appreciated that its presence in the reaction buffer would in general interfere with the interaction of antigen and antibody. As such, Applicant has submitted that SDS must normally be removed from a sample before an antigen-antibody reaction can be carried out. Therefore, Applicant has contended that, because it would be unexpected that a lysis buffer comprising SDS would be suitable for use as a reaction buffer, the claimed invention is distinguished from, and a non-obvious variant of the processes disclosed by the prior art.

Agreeably, the prior art teaches that concentrations of SDS in the range of 0.1-1% inhibit binding of an antibody to the antigen to which it would normally bind. For example, Qualtiere et al. (*J. Immunol.* 1977 Nov; **119** (5): 1645-1651) teaches, in general, SDS concentrations greater than 0.01% destroy almost all immunochemical reactivity between an antibody and antigen; see entire document (e.g., the abstract). Similarly, Dimitriadis et al. (*Anal. Biochem.* 1979 Oct 1; 98

(2): 445-451) teaches, although non-ionic detergents have little or no detectable effect, the anionic detergent SDS inhibits the reaction between antibody and antigen by more than 90%, when present at concentrations of above 0.2% (w/v); see entire document (e.g., the abstract). Finally, McCabe et al. (*J. Immunol. Methods.* 1988 Apr 6; **108** (1-2): 129-135) reports the finding that, whereas detergent extraction increased the ELISA response, relative to response from membrane suspensions, high concentrations of SDS interfered with the ELISA, and further discloses that such inhibitory effects were reduced by dilution of the extracts before adsorption of antigen on the microtitre wells; see entire document (e.g., the abstract). As a consequence of the recognized inhibitory effects of SDS upon antibody-antigen reactivity, some investigative work has focused upon elaboration of processes for removing SDS from samples comprising proteins prior to immunochemical analyses[1].

Apart from the specific mechanics of the active process that is claimed, which render the invention a non-obvious variant of the processes of the prior art, it is further noted that the overexpression of p16 by cervical intraepithelial neoplastic cells and cervical carcinomas is an unexpected phenomenon, otherwise taught only by U.S. Patent No. 6,709,832. p16 is a cyclin dependent kinase inhibitor, which is ordinarily inactive or underexpressed in cancer cells; therefore, p16 is generally thought of a tumor suppressor[2].

Therefore, it is concluded that the prior art does not teach or fairly suggest the claimed processes for detecting cervical intraepithelial neoplastic cells and cervical carcinomas in a subject by determining if p16 is overexpressed in the cells of a sample acquired from the subject, as compared to normal cervical cells, wherein such overexpression identifies cervical intraepithelial neoplastic cells and cervical carcinomas.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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[1] See, e.g., Bhakdi (*J. Biochem. Biophys. Methods.* 1980 Jan-Feb; **2** (1): 79-90); see entire document (e.g., the abstract).

[2] For a recent review of this topic, see, e.g., Liggett et al. (*J. Clin. Oncol.* 1998 Mar; 16 (3): 1197-1206).

Conclusion

6. Claims 1-6, 20, 21, and 23-28 have been allowed.

7. Claims 1-6, 20, 21, and 23-28 have been as claims 1-14, respectively.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
September 7, 2007